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09/215,257 12/18/98 FIRE

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EXAMINER

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1635

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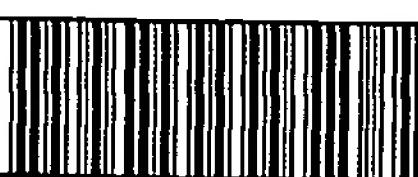
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Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary

Application No. 09/215,257	Applicant(s) Fire et al.
Examiner Karen A. Lacourciere	Group Art Unit 1635



Responsive to communication(s) filed on Dec 4, 2000

This action is FINAL.

Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle* 35 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire 3 month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claim

Claim(s) 1-35 and 39-42 is/are pending in the application.

Of the above, claim(s) 7 and 24 is/are withdrawn from consideration.

Claim(s) _____ is/are allowed.

Claim(s) 1-6, 8-23, 25-35, and 39-42 is/are rejected.

Claim(s) _____ is/are objected to.

Claims _____ are subject to restriction or election requirement.

Application Papers

See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

The drawing(s) filed on _____ is/are objected to by the Examiner.

The proposed drawing correction, filed on _____ is approved disapproved.

The specification is objected to by the Examiner.

The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

All Some* None of the CERTIFIED copies of the priority documents have been

received.

received in Application No. (Series Code/Serial Number) _____

received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____

Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

Notice of References Cited, PTO-892

Information Disclosure Statement(s), PTO-1449, Paper No(s). 5 and 15

Interview Summary, PTO-413

Notice of Draftsperson's Patent Drawing Review, PTO-948

Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

DETAILED ACTION***Election/Restriction***

Applicant requests clarification (response filed 12-04-00, page 4) as to the exclusion of subject matter drawn to plant cells from the examined subject matter. Given that the restriction of the claims was made final in the prior Office action (mailed 06-02-00) and a generic claim is not allowable at this time, the restriction is maintained and claims 7 and 24 are maintained as withdrawn. Upon finding a generic claim allowable, however, the examination will be extended to include methods for non-animal organisms and cells.

Applicant argues that the Examiner's statement that the origin of the cell will effect the success of the claimed methods is not valid, as evidenced by post-filing references. This seems to be an argument traversing the restriction. Whether or not the origin of the cell effects the claimed methods does not seem relevant to the restriction. The origin of cell would, however, result in methods which involve materially different steps, which supports the validity of the restriction set forth in the prior Office actions.

Response to Amendment

The rejection of claims 12 and 35 under 35 U.S.C. 112, second paragraph, set forth in the prior Office action (mailed 06-02-00), due to improper hyphenation and improper dependency, is withdrawn in view of Applicants amendments (filed 12-04-00).

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Response to Arguments

The rejection of claims 1-6, 8-23, 25-35 and 39 under 35 U.S.C. 112, first paragraph, set forth in the prior Office action (mailed 06-02-00) as containing subject matter which was not described in the specification is withdrawn in view of Applicants arguments (filed 12-04-00).

Applicant's arguments with respect to the rejection of claims 1-6, 8-23, 25-35 and 39 under 35 U.S.C. 112, first paragraph, as not being enabled by the specification have been considered but are moot in view of the new ground(s) of rejection.

New Grounds of Rejection

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-6, 8-23, 25-35, 39, 40 and claims dependent on said claims are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1-6, 8-23, 25-35, 39 and 40 are indefinite due to the recitation "a portion of the target gene of at least 25 nucleotides in length". The metes and bounds of the phrase "a portion

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of the target gene of at least 25 nucleotides in length" are unclear because it is unclear what length of nucleotides defines a "portion". It is noted that Applicant has amended the claims (amendments filed 12-04-00) to include a limitation of "at least 25 nucleotides in length" to overcome this rejection, however, as written, the phrase "at least 25 nucleotides in length" modifies the region of the target gene. The limitation provided by amendment does not limit the length of the RNA, as the RNA can be any "portion" of a target gene, wherein the target gene is at least 25 nucleotides long. This rejection would be overcome if the claims were amended to limit the length of the RNA to at least 25 nucleotides.

Claims 1, 39 and 40 are indefinite due to the recitation of an RNA molecule with a nucleotide sequence identical to the sequence of a target gene. A gene is composed of DNA, which differs from RNA sequences by incorporating thymidyl residues instead of uracil residues. As such, it is unclear how an RNA sequence would be identical in sequence to the DNA sequence of a target gene. For the purposes of examination of the instant case, this has been interpreted to mean an RNA molecule which comprises an RNA sequence which corresponds to the DNA sequence of a target gene, wherein the sequence corresponds to either (or both) the coding strand or the non-coding strand.

Claims 1, 39 and 40 are further indefinite because it is unclear whether the RNA comprises the identical nucleotide sequence, or if the double stranded region comprises the identical nucleotide sequence. For the purposes of the examination of the instant case, the claim has been interpreted as encompassing methods using either type of molecule.

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Claim 28 recites the limitation "the identical nucleotide sequence" in the first line of the claim. There is insufficient antecedent basis for this limitation in the claim.

Claim 33 is indefinite due to the recitation "wherein a genetically-engineered host organism transcribing the RNA comprises the food". As written, claim 33 is drawn to a method wherein the genetically-engineered host organism transcribing the RNA also contains the food which contains the RNA. This is unclear, given the methods contemplated in the instant specification and the fact that two RNA's would be administered to the target organism in the claimed method. This rejection would be obviated by amending this phrase to read "wherein the food comprises a genetically-engineered host transcribing the RNA."

Claim 35 recites the limitation "the expression construct", bridging lines one and two of the claim. There is insufficient antecedent basis for this limitation in the claim.

Claim 39 is further indefinite because the claim recites a kit comprising a means for introducing an RNA into a cell and describes an double stranded RNA, but does not actually recite that the RNA is a component of the claimed kit. For the purposes of the examination of the instant claims, it has been assumed that the RNA described is also a component of the claimed kit.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to

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make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-6, 10-23, 27-35 and 40-42 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for methods of inhibiting expression of a target gene using a double stranded RNA in nematode or in vitro, does not reasonably provide enablement for methods of inhibiting expression of a target gene using a double stranded RNA in any organism in vivo (whole organism). The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

The following factors have been considered in formulating this rejection (*In re Wands*, 858F.2d 731, 8 USPQ2d 1400 (Fed. Cir. 1988)): the breadth of the claims, the nature of the invention, the state of the prior art, the relative skill of those in the art, the predictability or unpredictability of the art, the amount of direction or guidance presented, the presence or absence of working examples of the invention and the quantity of experimentation necessary.

Claims 1-6, 10-23, 27-35 and 40-42 are drawn broadly to methods of inhibiting gene expression in any setting, in vitro or in vivo (whole organism), for any organism, including humans and other mammals. The claimed methods are further drawn to methods wherein the double stranded RNA of the claimed methods is administered by various routes, including injection, administration at a body cavity and by administering the double stranded RNA in food, including administering a transgenic organism which has been genetically manipulated to produce the

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double stranded RNA from a vector or producing the double stranded RNA in the target organism by expression of the double stranded RNA from a vector, which read on gene therapy methods.

The specification provides examples wherein double stranded RNA, with regions “identical” to several different target genes, is administered to *C. elegans* through various routes and the target gene is thereby inhibited. Applicant has provided a number of post-filing references which demonstrate similar methods applied to reduce expression of a variety of genes in *drosophila*. The specification does not provide any examples wherein their claimed methods are used to inhibit the expression of any gene in a mammal, including humans.

Methods of inhibiting gene expression using nucleic acids *in vivo*(whole organism) are highly unpredictable, mainly due to issues of how to specifically deliver a nucleic acid molecule or vector to a target cell at a concentration effective to result in a desired effect, and, in the case of gene therapy, the determination of target cell specific vectors and promoters to achieve and maintain expression of the gene., gene therapy methods (ie. nucleic acids expressed from a vector) are further hampered by unpredictable loss of expression (see for example Branch, Crooke, Anderson and Verma et al.). The specification states that the claimed methods differ from antisense methods by acting through a different, but undefined, mechanism. Despite the mechanism, the methods claimed require that an RNA, or vector expressing said RNA, be delivered specifically to a target cell in an organism *in vivo*(whole organism) at a concentration effective enough to inhibit the expression of a target gene, particularly at a concentration effective

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enough to inhibit the expression of a gene to the extent that the organism exhibits a "loss of function" phenotype. As such, although Branch, Agrawal(TIBTech), Verma et al. and Anderson discuss issues of delivery and expression in reference to antisense methods and gene therapy vectors expressing protein products, the same art recognized issues of enablement would apply to the instantly claimed methods. Specific embodiments of the claimed methods include delivery of the RNA of the claimed methods using food, including food comprising an organism expressing the RNA. This method of delivery would not be predicted to be effective, particularly in mammals, because the RNA would be degraded by digestive enzymes. The specification provides generic guidance with respect to delivery of double stranded RNA molecules, or vectors expressing such, into a cell *in vivo*(whole organism), however, the specification does not provide specific guidance that would enable one skilled in the art to overcome the art recognized unpredictability of specific delivery of nucleic acids (or vectors) to a target cell, or effective and sustained expression of a vector expressing such a nucleic acid.

Applicant has provided numerous post-filing references which support their assertion that the claimed methods can be applied successfully to a range of genes in several different organisms, particularly *C. elegans*, *drosophila* and other invertebrates. However, other examples demonstrate that in other organisms, including zebrafish and mice, the inhibition by double stranded RNA was unpredictable or transient (see for example Oates et al. (reference on PTO form 1449 filed 12-04-00) or Wianny et al. (reference on PTO 1449, filed 12-04-00)). Attempts to 'knock out' gene function in an organism using double stranded RNA administered at the

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embryonic stage have demonstrated that inhibition by double stranded RNA is transient, and function is regained after multiple cell divisions (see for example Wianny et al.). Further, mammals, including humans, have demonstrated an immune response triggered by even small amounts of double stranded RNA that would preclude the use of double stranded RNA *in vivo* (whole organism) and in *Xenopus* an endogenous dsRAD activity would predict that dsRNA methods would not be effective (see for example Wianny et al. page 74). This suggests that although post-filing references support the enablement of the claimed methods more broadly than the working examples presented in the instant specification, the claimed methods are not enabled over the full scope claimed. Metabolic differences between different organisms would not allow one skilled in the art to broadly apply the methods taught for *C. elegans* and other invertebrates successfully in every organism, particularly mammals.

To practice the methods claimed, over the full scope claimed, it would require undue trial and error experimentation for the skilled artisan. Such experimentation would include the determination of how to specifically deliver a double stranded RNA or a vector to a target cell at a concentration effective enough to inhibit the expression of a target gene or inhibit a gene to the extent that the phenotype is loss of function, the determination of an appropriate vector and enhancer-promoter combination for each target cell type “the search for such combinations is a case of trial and error for a given type of cell.” (see Verma, for example p 240, columns 2 and 3), how to overcome the effects of dsRNA induced immune response, how to prevent the transient

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inhibition of genes observed in embryo experiments, and the determination of how to implement these methods in organisms with dsRAD activity (and if these methods can be used at all).

Therefore, based on the breadth of the claims, the nature of the invention, the state of the art (beyond invertebrates), the high level of unpredictability in the art, the lack of specific guidance by the inventor (beyond *C. elegans*), the lack of working examples (beyond *C. elegans*), and the quantity of experimentation that would be required, it would require undue experimentation, beyond what is taught in the specification, to practice the methods as claimed, over the full scope claimed.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless --

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

(e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

Claims 1- 6, 8-11, 13, 17, 18, 22, 23, 25, 26, 28, 30, 31, 40 and 41 are rejected under 35 U.S.C. 102(b) as being anticipated by Agrawal et al.

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Agrawal et al. disclose methods of inhibiting the expression of a target gene in a cell, including a cell *in vivo* (whole organism), by administering an RNA molecule comprising a target hybridizing region, which is complementary to a sequence from a target gene and the complement of the target hybridizing region, and would, therefore, comprise an RNA sequence which is “identical” (corresponds to an identical DNA gene sequence) to a target gene. Agrawal disclose their methods wherein the target gene is a cellular gene, an endogenous gene, and a viral gene, including a viral gene which has been incorporated into the host genome, which would be encompassed by the term “transgene”. Agrawal further disclose their methods wherein the cell is from an invertebrate, including a nematode (see for example p 18, line 33), wherein the “identical” nucleotide sequence is 50 nucleotides long (see for example page 15, line 30) and wherein the expression of the target gene in a cell (*in vitro*) is inhibited by at least 10% (see for example experiments 1-3). Agrawal et al. provide for methods wherein the RNA is administered by extracellular injection or administered to a body cavity, outside the cell (see for example page 18, line 9).

Therefore, Agrawal et al. anticipates claims 1- 6, 8-11, 13, 17, 18, 22, 23, 25, 26, 28, 30, 31, 40 and 41.

Claims 1, 4-6, 11, 13, 21, 22, 23, 31 and 34 are rejected under 35 U.S.C. 102(e) as being anticipated by Draper et al.

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Draper et al. disclose methods of inhibiting the expression of a target gene in a cell, including a cell in vivo (whole organism) by administering an RNA comprising a double stranded structure (a ribozyme) and further comprising a sequence which is "identical" (corresponding RNA sequence) to the sequence of the non-coding strand of the target gene, including a viral gene incorporated into the cell genome (encompassed by the term "transgene"). Draper et al. disclose these methods wherein the region identical to the target gene comprises 25 or more nucleotides, wherein the RNA is produced in the cell from a vector, wherein the RNA is introduced by extracellular injection, and wherein the target gene is inhibited at least 10% in vitro (cell culture).

Therefore, Draper et al. anticipates claims 1, 4-6, 11, 13, 21, 22, 23, 31 and 34.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

The factual inquiries set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.

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2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

Claim 39 is rejected under 35 U.S.C. 103(a) as being unpatentable over Agrawal et al.

Claim 39 is drawn to a kit comprising means for introducing RNA into a cell. It is unclear whether the claimed kit also comprises a double stranded RNA (see the rejection of claim 39 under 35 U.S.C. 112, second paragraph), but it has been assumed that the double stranded RNA is also a component of the claimed kit. Agrawal et al. teach means for introducing RNA into a cell and teach a double stranded RNA, as claimed. Agrawal et al. do not claim the RNA and the means for introducing together in a kit. It would have been obvious to one of ordinary skill in the art, at the time the instant invention was made, to put the reagents taught by Agrawal et al. together in a kit because Agrawal et al. teach using these reagents together. One of ordinary skill in the art would have been motivated to make a kit comprising the double stranded RNA and the

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means for introducing RNA into a cell, as taught by Agrawal, for ease of use and convenience.

Therefore, the invention of claim 39 would have been obvious, as a whole, to one of ordinary skill in the art at the time the invention was made based on the teachings of Agrawal et al.

Conclusion

Any inquiry concerning this communication should be directed to Karen A. Lacourciere at telephone number (703)308-7523.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John LeGuyader can be reached at (703) 308-0447. The fax phone number for this Group is (703) 308-4242.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Karen A. Lacourciere
February 12, 2001

Remy Yucel
REMY YUCEL, PH.D
PRIMARY EXAMINER